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EXAMINER

LIU, SAMUEL W

ART UNIT	PAPER NUMBER
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1656

DATE MAILED: 11/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/674,408

Applicant(s)

ROEMISCH ET AL.

Examiner

Samuel W. Liu

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 25, 26 and 33-62 is/are pending in the application.
- 4a) Of the above claim(s) 25 and 26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 33-62 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☒ Certified copies of the priority documents have been received in Application No. 09/632,974.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>9/7/06</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of the claims

Claims 25-26 and 33-62 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 9/7/2006 has been entered.

The terminal disclaimer filed on 7 September 2006 disclaiming the terminal portion of any patent granted on this application, which would extend beyond the expiration date of US Pat. No. 6528299 which is parent co-pending application No. 11/11,8396 (see page 9 of "Remarks" filed 9/7/06) has been reviewed and is accepted. The terminal disclaimer has been recorded.

The amendment filed 9/7/06 which cancels claims 1-24 and 27-32 has been entered.

Claims 25-26 depend from the canceled claim 18. Therefore, claims 25-26 are withdrawn from further consideration by Examiner.

Claims 33-62 are therefore examined in this Office action.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

Withdrawal of the rejections

The provisional obviousness type double patenting rejection over 11118396 is now withdrawn in light of the terminal disclaimer filed (see above).

Objection to claims

- Claims 33, 36-48, and 51-62 are objected to as containing non-elected subject matter which is not the elected complexing agent of divalent ions.

- Claims 33-47 are objected to; in claim 33, “a pure form of proenzyme for the protease activating blood clotting factor VII” should be changed to “a pure form of proenzyme for the protease that activates blood clotting factor VII” because “protease activating” is easily misconstrued in this art and because the specification does not provide clear explain in this regard.

IDS

The references cited in the IDS filed 9/7/06 have been considered by Examiner.

New-Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 33-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 33 and 48 lack antecedent basis for “the protease”; this limitation does not indicate to which one (protease) the claims refer. The dependent claims are also rejected.

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Claim 48 recites "a mixture of a pure form of the protease ... and a pure form of a proenzyme ..."; the recitation is unclear as to whether or the proenzyme is activated by proteolytic action of the protease thereof on said proenzyme. The claims 49-62 depending from claim 48 are also rejected.

New- Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-62 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 33 and 48 are directed to composition comprising a precursor of protease (proenzyme) (claim 33) and both of the protease and the proenzyme (claim 48), respectively. The genus of the proenzyme polypeptide of claims 33 and the genus of protease polypeptide of claim 48 lack adequate written description for two reasons: 1) the full-length of amino acid sequences for the proenzyme and for the protease have not been described in the specification and in the claims; and 2) the open claim language ("... comprises the following peptide sequences...."), reads on a large genus, only partial sequences (four oligopeptides of SEQID NOs:1-4) of which is adequately described. Claims 33 and 48 and the dependent claims thereto are directed to polypeptides which are resulted from any random combinations (not in ordered sequence) of the four oligopeptide, e.g., a tandem covalent linkages of any combination of the oligopeptides thereof. The genus of claims 33 and 48 lack adequate written description because

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the open claims language (directed to the partial sequences) reads on full-length proenzyme and the protease which are not adequately described.

The Court of Appeals for the Federal Circuit has recently held that a “written description of an invention involving a chemical genus, like a description of a chemical species, ‘requires a precise definition, such as be structure, formula [or] chemical name,’ of the claimed subject matter sufficient to distinguish it from other materials.” *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant specification discloses SEQ ID NOs: 1-4 as subsequences of the proenzyme of a protease enzyme that activates blood clotting factor VII, or the protease which is post-translationally processed from said proenzyme; however, none of these four sequences disclosed are full length polypeptides; they are only partial amino acid sequences.

The specification fails to teach (i) what is structural relation of these four oligopeptides to the full-length polypeptide of the proenzyme or/and the protease; (ii) whether or not these oligopeptides are all or only some of them are presented in the proenzyme or the protease. Without these teachings, the skilled artisan are unable to predict the full-length proenzyme or

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protease from the disclosed oligopeptide sequences (wherein the full-length polypeptide contains said sequences).

This is not to say that applicants have not enabled one of skill in the art to obtain the full length polypeptide sequences using well-known PCR-cloning technology via primers derived from these sequences to clone out gene encoding the proenzyme and thus to obtain the peptide sequence thereof; this is to say that applicants have not described, directly or predictably, the sequences of the full-length proenzyme and full-length protease. Given the limited disclosure of structurally described species and the unpredictability of the art, applicants have failed to adequately describe a representative species of the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention, i.e., the composition comprising the full length polypeptides.

Moreover, since applicants do not fully describe a single full length polypeptide of any of the proteases (which *directly* or *indirectly* activate the factor VII), the addition of functional language in the instant claim, along with the retention of instant comprising language so as to read on the full length polypeptides, would not correct the defect of the instant claims because, to have adequate written description, the instant specification must contain a fully described, representative species (the full-length amino acid sequences) of the claimed genus as well as structure/function relationships between said fully described species and the other members of the genus.

Therefore, the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Enablement rejection

Claims 33-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 33 and 48 are directed to composition comprising a precursor of protease (proenzyme) (claim 33) and both of the protease and the proenzyme (claim 48), respectively. The instant specification fails to teach the full-length amino acid sequence of the proenzyme polypeptide of claims 33 and the full-length amino acid sequence of the protease polypeptide of claim 48. The claims and the specification only disclose partial sequence, i.e., four oligopeptides of SEQID NOs:1-4). The instant specification discloses SEQ ID NOs: 1-4 as subsequences of the proenzyme of a protease enzyme that activates blood clotting factor VII, or the protease which is post-translationally processed from said proenzyme; however, none of these four sequences disclosed are full-length polypeptides; they are only partial amino acid sequences. Also, the specification does not provide guidance or direction as to (i) what is structural relation of these four oligopeptides to the full-length polypeptide of the proenzyme or/and the protease; (ii) whether or not these oligopeptides are all or only some of them are presented in the proenzyme or the protease. Without the guidance or direction, the skilled artisan are unable to predict the full-length proenzyme or protease from the disclosed oligopeptide sequences (wherein the full-length polypeptide contains said sequences).

The instant disclosure does not satisfy enablement requirement of 35 U.S.C. §112, since without the full-length sequence, one skilled in the art is unable to make and use the claimed

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composition which requires the full-length sequences thereof. Claims 33 and 48 and the dependent claims thereto are directed to polypeptides which are resulted from any random combinations (not in ordered sequence) of the four oligopeptide, e.g., a tandem covalent linkages of any combination of the oligopeptides thereof. The open claims language (directed to the partial sequences) reads on full-length sequences of the proenzyme and the protease are not adequately described in the specification. Thus, the outcome of making functional proenzyme and the protease is unpredictable, and breath of the instant disclosure is broad than that is enabled, which do not allow one skilled in the art to make and use the claimed composition.

Without knowing the amino acid sequences for the above indicated the proenzyme and the protease thereof, one skilled in the art is unable to identify and characterized biological activity of the proenzyme and protease thereof, thereby to make and use the claimed composition comprising the proenzyme and the protease.

Scope enablement rejection

Claims 48-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the composition comprising proenzyme of a protease that activates blood clotting factor VII, does not reasonably provide enablement for the composition comprising both purified proenzyme thereof and the catalytically active protease (which is processed from precursor, i.e., the proenzyme). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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The application disclosure and claims have been compared per the factors indicated in the decision *in re* Wands 8 USPQ2d 1400, 1400 (Fed. Cir. 1998). These factors are considered when determining whether there is sufficient evidence to support a description that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. The factors include but not limited to: 1) the nature of the invention; 2) the breadth of the claims; 3) the predictability or unpredictability of the art; 4) the amount of direction or guidance presented; 5) the presence or absence of working examples; 6) the quantity of experimentation necessary; 7) the relative skill of those skilled in the art.

Each factor applicable is addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

(1) The scope of the claims/(2) The nature of the invention:

Claims 48-62 are directed to a composition comprising a purified proenzyme and protease which is enzymatically processed from the proenzyme thereof. The specification does not teach nor provide working example(s) for purification of the active protease.

Although there provides example for chromatographic purification for the *proenzyme* (page 10), the instant specification fails to teach or/and provide working example for purifying the enzymatically active *protease* thereof. The specification sets forth that the amino acid sequences of the protease has 100% sequence identity to that of the protein taught by Choi-Miura et al. (see page 1, the last three lines). Choi-Miura et al. teach that their PHBP protein is a heterodimer consisting of 50 and 17 KDa subunits (see abstract). Thus, chromatographic behaviors between the protease (heterodimer) and the proenzyme (non-dimer form) would be distinct/different. Since the purification mean set forth in specification (page 10) is applied to the

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proenzyme, the outcome of purifying the heterodimer form of the protease is not predictable.

This renders the instant claims not enabled to the full extent of their scope without undue experimentation.

The composition of claims 48-62 requires the presence (mixing) of both the protease and the proenzyme simultaneously. However, the specification fails to teach how to prevent the protease activating (proteolysing) the proenzyme assuming that the mature form, i.e., active protease (processed from the proenzyme) has ability of activating the proenzyme thereof. The example for this is that chymotrypsin can enzymatically act on chymotrypsinogen (see below in *section (3)* for the detail). Thus, a great deal of experimentation is needed to characterize the condition so as to allow for formulation of the proenzyme and the protease together without unpredictable “activation” or degradation of the proenzyme (the components of the claimed composition).

Furthermore, since the specification does not describe the full-length sequence of said protease, one skilled in the art would have construed that the protease mentioned in the specification (the third line from the bottom at page 1) is the matured protease but not the proenzyme (this is because that the specification has clearly used the term “proenzyme” throughout the instant disclosure to distinguish from the term “protease”). When characterizing the enzymatic activity of the protease, one would have hardly found activity inasmuch as said protease is inactive as being a proprotease. Hence, identifying property and function of the purified, in this regard, also requires undue experimentation.

(3) The unpredictability of the art:

It has been well-known that proprotease (proenzyme), e.g., chymotrypsinogen (a proenzyme) can be self-cleavage by protease that is processed from proprotease, e.g., chymotrypsin (see page 2685, the right column, lines 9-14, Velez et al. *Biophys. J.* (1998) 75, 2682-2697). Since the specification fails to teach processing (activating) the claimed proenzyme to the active protease, the outcome of “mixing” of the proenzyme and the protease together (claim 48) is highly unpredictable (in view of that the protease will “activate” the proenzyme in the composition to produce the protease, which “activation” would eventually result in no proenzyme coexistence with the activated protease). Therefore, stability and property of the claimed composition comprising both the proenzyme and the protease is unpredictable.

(4) The state of the prior art:

The general knowledge and level of skilled in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attribute and characteristics that identify (i) functional composition comprising both the proenzyme and the protease (wherein the proenzyme will not be enzymatically degraded by the protease), and (ii) parameters for purifying the active protease, the instant specification needs to provide omitted teaching or description in this regard in order for enabling the claimed invention.

(5) The quantity of experimentation necessary:

In the absence of working examples with regard to purifying the active protease and preparing the composition containing both the proenzyme and the protease, unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. The quantity of experimentation

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would be large and unpredictable (see above). One skilled in the art would be required to carry out undue experimentation for finding out proper mean to purify the bioactive protease and for screening and characterizing the composition that allows for productive formulation of both proenzyme and the protease together under the condition(s) that said protease does not activates or degrade the purified proenzyme.

(6) The relative skill of those in the art:

The general knowledge and level of skill in the art do not supplement the omitted description with respect to a massive number of variant sequences of peptide. In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a molecular biologist with several years of experience in enzymology and protein purification as well as knowledge in protein chemistry. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable. An unduly level of skill is needed for the skilled artisan in order to make and characterize the above-discussed composition comprising the proenzyme ad the protease, and develop a mean for purifying the enzymatically active protease.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Thus, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC §103

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 33-36, 38-39, and 43-47 are rejected under 35 U.S.C. 103(a) over as obvious over Choi-Miura et al. (*J. Biochem.* (1996) 119, 1157-1165) in view of Turner et al. (US Pat. No.5326558).

Choi-Miura et al. teach 560 amino acid hyaluronan-binding protein (PHBP) polypeptide comprising the instant peptide sequences of SEQ ID NOs: 1-4 (see Figure 3). While Choi-Miura et al. teach purifying their PHBP, slight impurities are noted (see page 1162, the left column). However, Choi-Miura et al. clearly indicate purifying the PHBP protein and describe means thereof (see page 1162, the left column). One skilled in the art would have purified PHBP in accordance with the Choi-Miura' method with reasonable expectation of success. Thus, this renders purification of their PHBP proenzyme (in pure form) obvious. The Choi-Miura et al. teachings therefore is applied to claim 33.

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Choi-Miura et al. teach the eluent (composition) comprising the purified PHBP from HA-Sephacrose column contains glycine (see page 1161, the left column), as applied to claims 39 and 45.

Said the eluent contains mini-amount albumin (see page 1162, the left column), as applied to 46.

Claim 47 recites "*the composition acts as a biological test reagent*"; this recitation is considered to be an intended use which has no patentable weight to the claimed composition. Therefore, the above Choi-Miura et al. teachings are applied to the composition of claim 47.

Choi-Miura et al. do not expressly teach that the composition comprises complexing agent (e.g., EGTA or EDTA), and compound (e.g., aprotinin) for preventing protein degradation.

Yet, Choi-Miura et al. have discussed that the purified PHBP is susceptible to cleavage by proteolytic enzymes (see page 1162). It is well known that EGTA or EDTA and protease inhibitor compound, e.g., aprotinin, are routinely used in the protein purification procedure to prevent the purified protein/enzyme from proteolytic degradation. Turner et al. teach a cocktail comprising protease inhibitors (aprotinin, leupeptin, ethylene glycol-bis-tetraacetic acid (EGTA) which was added to the sample containing the protein that is subject to purification in order to minimize proteolysis (see column 13, lines 2-8), which is applied to claims 34-36, 38 and 43-44.

One of ordinary skill in the art at the time the invention was made would have been motivated to formulate the composition with the above-mentioned protease inhibitory compounds. This is because Choi-Miura et al. already stated the problem regarding degradation of PHBP protein by the proteolytic enzyme, and because those protease inhibitory compounds

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are known and routinely used by the skilled artisan in order to reduce or minimize the proteolysis of protein of interest (here it is the purified PHBP protein), as is noted by Turner et al. reference.

Therefore, the claimed invention was *prima facie* obvious to make and use the invention at the time it was made.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is 571-272-0949. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr, can be reached on (571) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval IPAIRI system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAG only. For more information about the PAN system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Samuel Wei Liu, Ph.D.

Art Unit 1656, Examiner



KATHLEEN M. KERR, PH.D.
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